For Amendment 6 to: RTOG 0618, Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

NCI/Local Protocol #: RTOG-0618/RTOG 0618

NCI Protocol Version Date: March 6, 2014

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.</td>
</tr>
</tbody>
</table>
| Title pages | • On the 1st title page, the affiliation and contact information for the Medical Oncology and Translational Research Co-Chairs were updated.  
  • On the 2nd title page, this amendment and the study closure date were added to the Document History table.  
  • On both title pages, as required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”. |
| Schema page | As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”. |
| 6.10.1      | In the 2nd paragraph, the date and link for the NCI Guidelines were updated. |
| Informed Consent | No changes |
RTOG 0618, “Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer”

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

RTOG 0618 has been updated as follows:

1st title page: “Study Chairs” was updated to the current RTOG standard text, “Study Team”, and the Senior Statistician was updated from Dr. Bae to Dr. Hu. In addition, the Activation, Closure, Update, and Version Dates were moved to a Document History table to update the protocol to current RTOG standards.

A 2nd title page was created in order to add a Document History table, and the version date of the protocol was bolded in the table to update the protocol to current RTOG standards. In addition, this update was included in the table.

Schema page, footnote 5: The phrase, “or pneumonectomy are” was corrected to “or pneumonectomy is”.

Section 5.3.1: The link to the CTSU IRB/REB Certification Form was updated.

Section 6.10:
- In the 2nd paragraph, the parenthetical reference to the NCI Guidelines was updated.
- In the 4th paragraph, the phrase, “including a male patient’s impregnation of his partner”, was added to the last sentence to update the protocol to current RTOG text.
- In the 2nd paragraph of “AdEERS Reporting Requirements”, the link to CTCAE, v. 4 was updated.
- The table under “Adverse Events and Serious Adverse Events” was updated to the current NCI standard.

Section 10.1.3: The shipping and postal addresses for the RTOG Biospecimen Resource were updated. This change also was made in Section 10.3.3 and in Appendix VI.

Section 10.5: The 3rd paragraph was updated to current RTOG standard text.

Section 10.6: The link to the Patient Tissue Consent Frequently Asked Questions was updated.

Appendix I:
- Under “About Using Tissue and Blood for Research”, the link to the information sheet was updated.
- Under “Where can I get more information”, the TTY number was deleted as requested by CTEP.

Appendix II: The timeframe for the collection of the first urine and blood was corrected to “within 3 days before the 1st SBRT dose” to be consistent with Section 10.4.
**SUMMARY OF CHANGES**

**Amendment 5, Version Date: December 9, 2010**

(Broadcast: 12/16/10)

**RTOG 0618**, "Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer"

**Study Chair**: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

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**RTOG 0618** has been amended as follows:

As mandated by CTEP, **Section 6.10.1** has been amended to require the use of CTCAE, version 4 for grading of all adverse events as of January 1, 2011.

Note: REFERENCES to CTCAE, v. 3.0 remain in the protocol. These are appropriate, as treatment decisions for patients enrolled on this study were based on that version.

**Other Changes**

**Section 6.10.2**: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.
SUMMARY OF CHANGES
Update Date: April 13, 2010

RTOG 0618, "Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer"

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

Eligibility Checklist, page 3: Questions 18 and 19 were labeled "inactivated" and Questions 20-27 were re-ordered for database purposes. No changes were made to eligibility criteria.
SUMMARY OF CHANGES
Amendment 4, Version Date: March 25, 2010
(Broadcast 4/13/10)

RTOG 0618, "Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer"

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

RTOG 0618 has been amended as follows:

1. Recurrence definitions have been amended to appropriately reflect initial staging.

In a review of the manuscript describing the conduct of RTOG 0236 (SBRT in medically inoperable lung cancer) by the Journal of the American Medical Association (JAMA), the editors correctly pointed out that unconventional definitions of local control were used, which described only recurrence of the primary treated tumor. The editors indicated that failure within the involved lobe (part of the T-stage for lung cancer in the TNM system) should be considered a component of local control. The editors indicated that recurrence definitions should reflect upon the site's TNM staging. As such, a recurrence of the original primary tumor (originally characterized by the T of the TNM staging) is deemed a local recurrence. A recurrence in the primary tumor's draining lymph nodes (hilar and mediastinal as originally characterized by the N of the TNM staging) is deemed a regional recurrence. Finally, a recurrence in distant sites (originally characterized by the M of the TNM staging) is deemed a disseminated recurrence. Fortunately, in 0236, the specific patterns of recurrence within the lungs were collected, and the oversight was corrected. In a re-analysis of 0236, 3 additional patients had new nodules within the same lobe and were included in the local recurrence definition. The primary endpoint was more correctly stated as "primary tumor control" (not local control), this nomenclature was corrected throughout the 0236 manuscript, and actuarial data on local control defined as primary tumor control plus control within the same (involved) lobe as well as local-regional control was added.

RTOG 0618 used the same unconventional recurrence definitions as RTOG 0236. Therefore, the protocol has been amended and patterns of recurrence have been reclassified appropriately. The terms "local control" and "local failure" as related to study procedures (not introduction) have been changed to "primary tumor control" and "primary tumor failure" throughout the protocol. The following sections were amended for this change: Schema page, Sections 1.5, 1.7 (title of 3rd column in table), 1.8 (last paragraph), 2.1, 2.2.4, 11.2.1, 11.2.3, 13.1.1, 13.1.2, 13.2.1, and 13.3.2.
2. Patient follow up has been amended to the current RTOG standard of the patient's lifetime. With follow up for the patient's lifetime, sites are asked to perform yearly toxicity assessments and CT scans for assessment of efficacy (control), since these patients have a roughly 20% risk of developing a second primary cancer in addition to a risk of having failure of the protocol therapy. The following sections were amended for this change: 11.2.4; 12.1 (the schedule for the Follow-up Form); Appendix I (under "When I am finished taking SBRT" and "How long will I be in the study?"); and Appendix II (last column added under "Follow Up").

Other Changes
Eligibility Checklist, page 3: Questions 1, 2, 3, 4, 5, 7, 10, 12, 14, 15, and 18-24 of this demographic portion of the checklist were amended to current RTOG standard.

Section 3.1.4: The 5th bulleted item was amended to clarify existing eligibility requirements regarding blood oxygen and carbon dioxide. These changes do not constitute a change to the study design.

Section 5.1.2: The e-mail address for the ITC was updated. This change also was made in Sections 12.2 and 12.2.1.

Appendix I:

- Under "What are my rights if I take part in this study", the 3rd paragraph concerning a Data Safety Monitoring Board was added to update the consent to current RTOG standard.
- Under "Where can I get more information?", the URL for the NCI's general information web site was updated.
SUMMARY OF CHANGES
Amendment 3, Version Date: August 20, 2009
(Broadcast 9/17/09)

RTOG 0618. "Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer"

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651;
Robert.Timmerman@UTSouthwestern.edu

RTOG 0618 has been amended as follows:

The timeframe for required histological confirmation of NSCLC was expanded from 90 days to 180 days in an effort to capture more patients ideal for this trial. Screening failures have resulted from the 90 day confirmation timeframe, and repeat biopsy is impractical. Routine work up of a solitary pulmonary nodule at some institutions, especially those in underserved areas such as county hospitals in large cities, takes several months. This change was made in question 1, page 1 of the Eligibility Checklist, in Section 3.1.1, and in the 1st column under "Pre-registration" in Appendix II.

The required timeframe in Section 6.1.2 for completion of treatment was expanded from 14 days to 16 days to be more consistent with the other requirement in this section that treatments be separated by a maximum of 8 days.

Other Changes

Title Page: The Senior Statistician's affiliation was amended to current RTOG standard text and her e-mail address was updated.

Eligibility Checklist, page 3: Questions 18-20 were reformatted to current RTOG standard text. The corresponding questions in Appendix I, under "About Using Tissue, Urine, and Blood for Research", were reformatted to be consistent.

Section 3.1.4: The 5th bulleted criterion for determining candidates for surgical resection, "exercise oxygen consumption > 50% predicted", was deleted. The equipment and expertise required to conduct this test is no longer routinely available at enrolling institutions. The remaining criteria for medical operability are adequate without this test.

Section 4.0: The 2nd "Note" concerning patients being offered the opportunity to participate in the correlative components of the study was deleted, as this note is provided in Section 10.0, as is current RTOG standard.

Section 5.1: The last sentence was added to the section to amend it to current RTOG standard text.
Section 5.2.1 was amended to current RTOG standard text.

Section 5.3.2 was amended and Section 5.3.3 was added to amend "Regulatory Pre-Registration Requirements" to current RTOG standard text.

Section 5.4.1: In the 5th paragraph, the e-mail for RTOG web support was updated.

In the heading of Section 6.9, the word, "Therapy", was added to amend to the heading to current RTOG standard text.

Section 6.10.1: The 1st paragraph was amended and the 5th & 6th paragraphs were added to amend this section to current RTOG standard text. In addition, under "AdEERS Reporting Requirements", the 3rd paragraph was amended and the 4th paragraph added to amend this section to current RTOG standard text.

Appendix III: The Karnofsky Performance Scale was deleted, and in the Zubrod Performance Scale table, parenthetical REFERENCES to Karnofsky scores were deleted, as the Zubrod is the performance scale being used in the study.

Appendix VI: In the shipping address at the end of "Urine Collection Kit Instructions", "DHL" was replaced with "UPS" to be consistent with changes made in a previous amendment.
SUMMARY OF CHANGES
Update Date: May 7, 2009
(Broadcast 5/7/09)

RTOG 0618, "Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer"

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

At the request of the RTOG Biospecimen Resource and the Translational Research Co-Chair, Dr. Kong, the logistics for submission of specimens in RTOG 0618 have been updated as follows:

- **Section 10.1.1.1**: The word, "preferred", was added after "tissue block of tumor" as information for sites.
- **Section 10.1.2.4**: In the "Note", the temperature was corrected from -20° to -80° C.
- **Section 10.1.3**: "Mailing Address" was clarified to "U.S. Postal Service Mailing Address", and "DHL" was updated to "UPS" in the Courier Address. These changes also were made in Appendix VI.
- **Section 10.3.1**: A note was added to inform sites that a blood collection kit can be obtained from the Biospecimen Resource. This information also was added in Appendix VI.
- **Section 10.3.2** was updated to clarify that the Specimen Transmittal Form must document the date of collection of plasma and buffy coat, as well as serum.
- **Section 10.3.3**: Blood samples for translational research will be sent to the RTOG Biospecimen Resource rather than to Dr. Kong. The shipping address and contact information for questions were updated accordingly in this section and in Appendix VI.
- **Section 10.4**: In the 2nd column, "Specimens collected when", the timeframes for collection of urine and blood were clarified from "Within 3 days of the first dose of SBRT" to "Within 3 days before the first dose of SBRT". This clarification also was made in Appendix VI.
- **Section 10.5**: The last 3 paragraphs referring to submission of blood samples to Dr. Kong were deleted, and the remaining text regarding reimbursement and confirmation of appropriate materials was reorganized for clarity.
- **Appendix VI**:
  - The 2nd sentence regarding disposal of the Plug Kit was deleted to update the appendix to current Biospecimen Resource standard text.
  - In the 2nd paragraph under "Shipping instructions for urine specimens", the 2nd sentence was corrected to "Specimens should be shipped only Monday through Wednesday…"
In the "Note" under "Shipping instructions for urine specimens", the phrase, "and there is sufficient ice for shipment" was added as an instruction to sites.
SUMMARY OF CHANGES
Amendment #2, Version Date: February 4, 2009
(Broadcast on 3/12/09)

RTOG 0618, Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651;
Robert.Timmerman@UTSouthwestern.edu

RTOG 0618 has been amended to lower the baseline FEV1, allow dose painting delivery techniques including IMRT, and permit sublobar or wedge resections as follows:

Title Page: The statistician's name and contact information were added.

Schema: Footnote # 5 was changed to allow sublobar or wedge resections per the local surgeon's discretion. Patients of borderline resectability (still medically operable) may not be ideally treated with a lobectomy or pneumonectomy depending on their circumstances even for primary off protocol therapy. In addition, after SBRT, there may be lung injury that precludes lobectomy or pneumonectomy even if such procedures were feasible prior to enrollment.

Eligibility Checklist: Question # 21 on page 3 of 3 was added for consistency with IMRT being added.

Section 3.1.4: The baseline FEV1 was changed to > 35% predicted and the diffusion capacity was changed to > 35% predicted. With modern surgical approaches, it has become customary to offer surgery to patients with this level of pulmonary function. The protocol wishes to include the reasonable spectrum of operable patients.

Sections 4.0 and 10: Text was added to emphasize that patients must be offered the opportunity to participate in the correlative components of the study.

Section 5.1: The heading was changed to "Pre-registration requirements for SBRT" for clarity.

Section 5.1.1: The logistics for submitting the Facility Questionnaire for SBRT were updated.

Section 5.1.3: New second and fourth sentences were added to incorporate IMRT.

Section 5.2: This new section was added to provide the pre-registration requirements for IMRT. The old Section 5.2, "Registration" was renumbered as Section 5.4.

Section 5.3.2: The old section 5.3.2 was deleted as it is not needed. It was replaced with
this new section to clarify pre-registration requirements for non-Canadian international institutions. Original Section 5.3.2.2 was renumbered as Section 5.3.2.3 as a result.

**Section 6.0**: The note that stated IMRT was not allowed was deleted, and a note allowing dose painting delivery techniques including IMRT was added.

**Section 6.2.1**: "Betatrons or microtron accelerators" were deleted in the first sentence as this type of equipment is obsolete.

**Section 6.2.2**: Text was added to the end of the first sentence and a new sentence was added to the end of the section for clarity. The platforms that use dose painting techniques have validated their beam output for smaller than the previously stated limits of field size.

**Section 6.2.4**: A new section describing acceptable treatment platforms was added in order to add to the scope of platforms available to carry out this treatment in line with the availability at experienced centers.

**Section 6.10.1**: At the end of the first paragraph, the NCI Guideline citation was updated; at the end of the second paragraph, a new sentence was added regarding pregnancy.

**Appendix II**: Footnote # 5 was added to follow up PET or biopsy at 6 weeks post SBRT.
RTOG 0618, Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

Study Chair: Robert D. Timmerman, M.D.; 214-645-7651; Robert.Timmerman@UTSouthwestern.edu

RTOG 0618 has been updated as follows:

Section 10.3.3 and Appendix VI: The address for the submission of blood to Dr. Kong has been updated.

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as an amendment.
RTOG 0618 has been amended to change biopsy timeframe and FEV eligibility and to clarify CT as follows:

Eligibility Checklist (pages 1-2 of 3): Question # 1 was changed to 90 days from 60 days for consistency with the change made to Section 3.1.1 (see below). Question # 7 was deleted, and subsequent questions renumbered, as a result of the deletion of Section 3.1.5 (see below).

Section 3.1.1: The timeframe for histological confirmation was increased to 90 days prior to registration in order to avoid the need for repeat biopsy of patients enrolled at county and VA hospitals where longer periods between diagnosis and start of therapy are common. Since patients are staged with PET and CT within 45 days of enrollment, this additional time since biopsy should not affect the study endpoints and should facilitate enrollment to this study.

Section 3.1.5: This section was deleted because in screening patients for RTOG 0618, it was pointed out by accredited institutions that an FEV-1 of 1.5 L can be normal in some patients (e.g., older women with small body habitus). As it is the intention of the protocol to enroll patients with normal pulmonary function, this eligibility criteria conflicts with the study design. Furthermore, the protocol has a better assessment of expiratory volume status pulmonary function already in place by using the percent predicted criteria of Section 3.1.4. Subsequent sections were renumbered as a result of this section being deleted.

Section 3.1.10.2 (old Section 3.1.11.2): The phrase “primary tumor dimension will be measured on CT” was deleted because this staging CT will not be used for pretreatment tumor dimensions (instead the treatment planning scan done closer to the actual time of treatment will be used for baseline tumor measurements). A new last sentence was added to accommodate sites with a combined PET/CT in which the CT part of the PET/CT is of diagnostic quality and read by a trained radiologist thereby avoiding duplication of staging studies.

Section 5.3: This was added to clarify regulatory pre-registration requirements.

Section 6.8: The number of cases to be reviewed was corrected for consistency with number of cases in the study.

Section 6.10.1: MedDRA version 9.0 was added to second paragraphs of AdEERS Reporting Requirements and RTOG Reporting Requirements.

Section 10 and Appendix VI: These were updated to reflect the move of the RTOG tissue bank to the RTOG Biospecimen Resource at University of California San Francisco.

Section 10.5: In the last paragraph, “Attn: Linda Bomba” was deleted as addressing invoices to “Clinical Trials Administration” is sufficient.

Section 10.6: The web link was updated.
Section 12.2: (DD) was added after the table heading “Preliminary Dosimetry Information.”

Section 13.4: The headings for this section and the table have been updated.